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61/484,317 10 May 2011 (10.05.2011) US(71) Applicant (for all designated States except US): **INDIANA UNIVERSITY RESEARCH AND TECHNOLOGY CORPORATION** [US/US]; 351 West 10th Street, Indianapolis, IN 46202 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **COOK, Silas** [US/US]; 3098 Chase Lane, Bloomington, IN 47401 (US). **ZHU, Chun-Yin** [CN/US]; 1213 South Paper Birch Court, Bloomington, IN 47403 (US).(74) Agents: **KEYES, William, John** et al.; Klintworth & Rozenblat IP LLC, 850 West Jackson Boulevard, Suite 660, Chicago, IL 60607 (US).

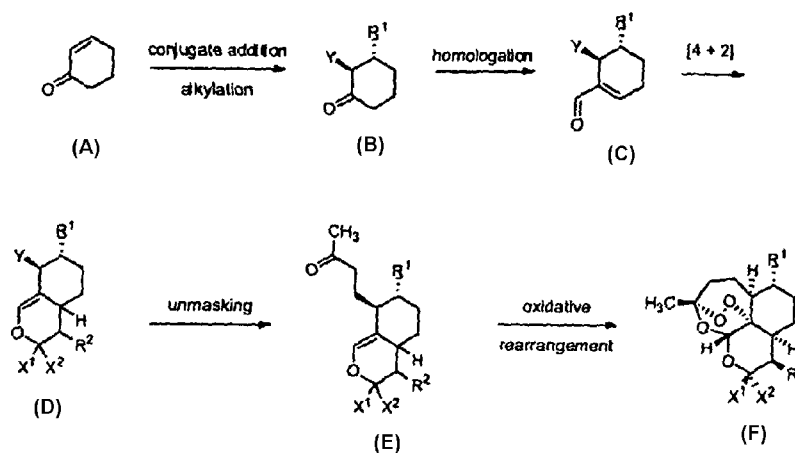
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(54) Title: TOTAL SYNTHESIS OF ARTEMISININ



(57) Abstract: The present invention provides a method for manufacturing artemisinin and its congeners from cyclohexenone as a starting material.

TOTAL SYNTHESIS OF ARTEMISININ

BACKGROUND

[001] Malaria infects over 200 million people each year with up to one million, mostly children, perishing from the infection [1]. Currently, the most effective treatment against malaria-causing *Plasmodium* parasites is artemisinin-based combination therapy (ACT). The key ingredient for the production of ACTs, artemisinin (**1**), is a natural product extracted on industrial scale from the sweet wormwood plant, *Artemisia annua*. Unfortunately, artemisinin is currently too expensive to meet the distribution needs of the world. Moreover, crop disruptions caused by natural disasters, poor planning and geopolitical events have led to shortages and price fluctuations. In the decade leading to 2012, there have been two primary approaches to combat these problems: using synthetic biology to produce a chemical precursor of artemisinin in microbes [2, 3], or breeding new varieties of *Artemisia annua* with improved growth and/or production traits [4]. While advances have been made in both areas, these strategies have yet to make a contribution to the world's artemisinin supply. Interestingly, the literature over the last decade reveals a disappointing lack of effort focused on discovering a *de novo* synthesis of **1** and its derivatives from inexpensive, readily available chemicals – a significantly more affordable and timely research proposition.

[002] Soon after the initial report of the structure and anti-malarial activity of artemisinin (**1**), chemists began working towards a feasible chemical synthesis of the unprecedented endoperoxide-containing natural product [7]. This work culminated in several total syntheses of artemisinin (**1**) between 1979 and 1996 [6, 8-15]. While impressive from a chemical “proof-of-principle” perspective, these early syntheses have done little to address the supply problems of artemisinin (**1**) because of the high costs inherent to long reaction sequences, excessive protecting group schemes and expensive terpene-based starting materials (Figure 1). Even modern syntheses of artemisinin (**1**) cannot compete on price with isolation from natural sources [16]. These problems have driven the perception that a laboratory synthesis of artemisinin (**1**) is untenable [17].

FIGURES

[003] Figure 1 illustrates the structure of artemisinin (1) and the various terpene starting materials used in previous total syntheses.

[004] Figure 2 illustrates a synthesis of (1).

5 DEFINITIONS

[005] As used herein, the terms "a" and "an" include singular as well as plural references unless the context clearly dictates otherwise.

[006] As used herein, the term "MVK equivalent" refers to a reactant used to functionalize a molecule in such a way as to allow future access to a moiety having
10 formula $-\text{CH}_2\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$. As methyl vinyl ketone (MVK) can be difficult to employ due to its tendency to polymerize, MVK equivalents are usually employed as surrogates for MVK itself. Typically, a molecule is first reacted with a MVK equivalent to yield an intermediate bearing a moiety of formula Y, where Y is a "masked MVK moiety." The masked MVK moiety is then "unmasked," *i.e.* subjected
15 to further transformation(s) to transform it into moiety $-\text{CH}_2\text{CH}_2-\text{C}(\text{O})-\text{CH}_3$. The masked MVK moiety may be unmasked right after the reaction with the MVK equivalent or at a later stage in the synthesis of a desired product. Example MVK equivalents include crotyl bromide and the molecules depicted in Table 1.

[007] As used herein, the term "alkyl" refers to a straight or branched chain
20 hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

[008] As used herein, the term "cycloalkyl" refers to a monocyclic, bicyclic, tricyclic,
25 spirocyclic, or polycyclic cycloalkyl. The monocyclic cycloalkyl is a carbocyclic ring system containing 3, 4, 5, 6, 7, or 8 carbon atoms and zero heteroatoms as ring atoms, and zero double bonds. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl is exemplified by a monocyclic cycloalkyl fused to a monocyclic
30 cycloalkyl. Representative examples of bicyclic cycloalkyls include, but are not limited to, bicyclo[4.1.0]heptane, bicyclo[6.1.0]nonane, octahydroindene, and

decahydronaphthalene. The monocyclic and the bicyclic cycloalkyl groups of the present invention may contain one or two alkylene bridges of 1, 2, 3, or 4 carbon atoms, wherein each bridge links two non-adjacent atoms within the groups.

Examples of such bridged cycloalkyls include, but are not limited to,

5 bicyclo[3.1.1]heptyl (including but not limited thereto, bicyclo[3.1.1]hept-2-yl), bicyclo[2.2.1]heptyl, bicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, adamantyl (tricyclo[3.3.1.1^{3,7}]decane), and noradamantyl (octahydro-2,5-methanopentalene). Spirocyclic cycloalkyl is exemplified by a monocyclic or a bicyclic cycloalkyl, wherein two of the substituents on the same carbon atom of the
10 ring, together with said carbon atom, form a 4-, 5-, or 6-membered monocyclic cycloalkyl. An example of a spirocyclic cycloalkyl is spiro[2.5]octane. The monocyclic, bicyclic, and spirocyclic cycloalkyl groups of the present invention can be appended to the parent molecular moiety through any substitutable carbon atom of the groups.

15 [009] The term "heterocycle" or "heterocyclic," as used herein, refers to a monocyclic, bicyclic, tricyclic, or polycyclic ring system. Monocyclic ring systems are exemplified by any 3- or 4-membered ring containing a heteroatom independently selected from oxygen, nitrogen and sulfur; or a 5-, 6-, 7- or 8-membered ring containing one, two or three heteroatoms wherein the heteroatoms
20 are independently members selected from nitrogen, oxygen and sulfur. The 5-membered ring has from 0-2 double bonds and the 6-, 7-, and 8-membered rings have from 0-3 double bonds. Representative examples of monocyclic ring systems include, but are not limited to, azetidiny, azepiny, aziridiny, diazepiny, 1,3-dioxolany, dioxany, dithiany, furyl, imidazolyl, imidazolinyl, imidazolidinyl,
25 isothiazolyl, isothiazolinyl, isothiazolidinyl, isoxazolyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolyl, oxadiazolinyl, oxadiazolidinyl, oxazolyl, oxazolinyl, oxazolidinyl, piperaziny, piperidiny, pyranly, pyraziny, pyrazolyl, pyrazolinyl, pyrazolidinyl, pyridyl, pyrimidinyl, pyridaziny, pyrroly, pyrrolinyl, pyrrolidinyl, tetrahydrofurany, tetrahydrothienyl, tetraziny, tetrazolyl, thiadiazolyl, thiadiazolinyl,
30 thiadiazolidinyl, thiazolyl, thiazolinyl, thiazolidinyl, thienyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranly, triaziny, triazolyl, and trithiany. Bicyclic ring systems are exemplified by any of the above monocyclic ring systems fused to an aryl group as defined herein, a cycloalkyl group as defined

herein, or another heterocyclic monocyclic ring system. Bicyclic ring systems can also be bridged and are exemplified by any of the above monocyclic ring systems joined with a cycloalkyl group as defined herein, or another non-aromatic heterocyclic monocyclic ring system. Representative examples of bicyclic ring systems include but are not limited to, for example, benzimidazolyl, benzoazepine, benzothiazolyl, benzothienyl, benzoxazolyl, benzofuranyl, benzopyranyl, benzothiopyranyl, benzodioxinyl, 1,3-benzodioxolyl, cinnoliny, 1,5-diazocanyl, 3,9-diaza-bicyclo[4.2.1]non-9-yl, 3,7-diazabicyclo[3.3.1]nonane, octahydro-pyrrolo[3,4-c]pyrrole, indazolyl, indolyl, indoliny, indoliziny, naphthyridiny, isobenzofuranyl, isobenzothienyl, isoindolyl, isoindoliny, isoquinoliny, phthalaziny, pyranopyridyl, quinoliny, quinoliziny, quinoxaliny, quinazoliny, 2,3,4,5-tetrahydro-1H-benzo[c]azepine, 2,3,4,5-tetrahydro-1H-benzo[b]azepine, 2,3,4,5-tetrahydro-1H-benzo[d]azepine, tetrahydroisoquinoliny, tetrahydroquinoliny, and thiopyranopyridyl.

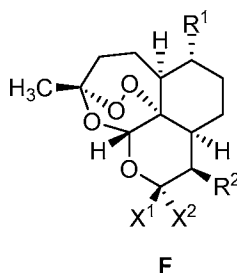
[0010] As used herein, the term "aryl," refers to a monocyclic-ring system or a polycyclic-ring system wherein one or more of the fused rings are aromatic. Representative examples of aryl include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl.

[0011] As used herein, the term "carboxyalkyl" refers to a carboxy group appended to the parent molecular moiety through an alkyl group as defined herein.

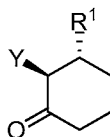
[0012] As used herein, the term "silyl ketene acetal" is a molecule bearing a moiety of formula $-C=C(OSiR^c)(OR^d)$. Representative examples include molecules where the R^c moieties are each an alkyl group, and R^d is also an alkyl group.

SUMMARY OF THE INVENTION

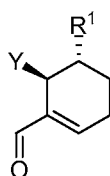
[0013] In one aspect, a method for manufacturing molecules of Formula F is provided:



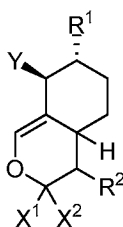
[0014] the method comprising the steps of: forming a mixture by mixing ingredients comprising cyclohexenone, an alkylating agent, and an MVK equivalent, to form a first synthetic intermediate of Formula B:

**B**

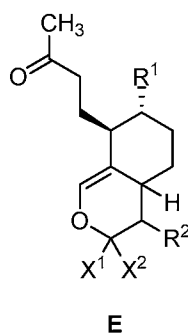
- 5 [0015] wherein R¹ is an alkyl moiety and Y is a masked $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$ moiety; homologating the intermediate of Formula B to an aldehyde intermediate of Formula C:

**C**

- [0016] forming a mixture by mixing ingredients comprising the intermediate of
10 Formula C and a dienophile, to form an intermediate of Formula D:

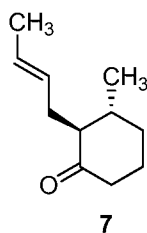
**D**

- [0017] wherein: R² is selected from the group consisting of -H, alkyl, cycloalkyl, heterocycle, and aryl, and at least one of X₁ and X₂ is selected from the group consisting of -H, -OH, -OCH₃, -OCH₂CH₃, -OSiR', -OR'', and carbonyl oxygen,
15 wherein R' is alkyl and R'' is alkyl; converting moiety Y to a $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$ group, to form an intermediate of Formula E, and

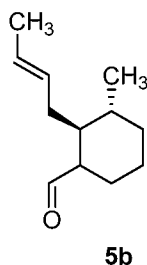


[0018] forming a mixture by mixing ingredients comprising the intermediate of Formula E, hydrogen peroxide, and a metal catalyst.

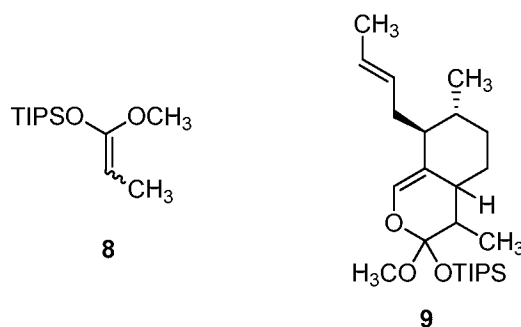
[0019] In another aspect, a method for manufacturing artemisinin is provided, comprising the steps of: forming a mixture by mixing ingredients comprising cyclohexenone, a methylating agent, and crotyl bromide, to form a first synthetic intermediate of Formula 7:



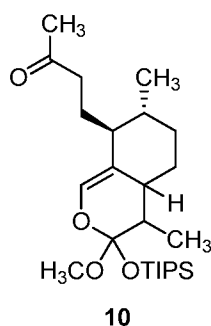
[0020] homologating the intermediate of Formula 7 to an aldehyde intermediate of Formula 5b:



[0021] forming a mixture by mixing ingredients comprising the intermediate of Formula 5b and a compound of Formula 8, to form an intermediate of Formula 9:

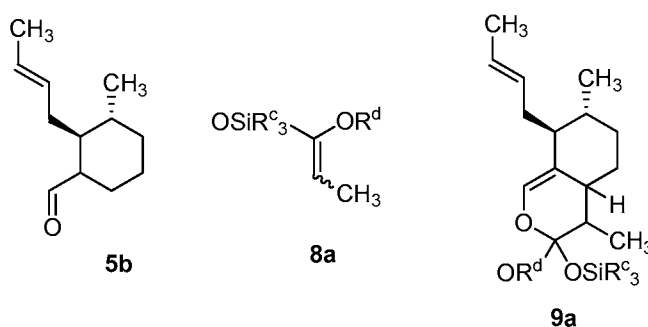


[0022] forming a mixture by mixing ingredients comprising the intermediate of Formula 9, hydrogen peroxide, and a palladium catalyst, to form an intermediate of Formula 10:

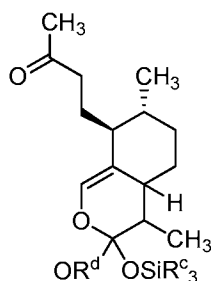


[0023] and forming a mixture by mixing ingredients comprising the intermediate of Formula 10, hydrogen peroxide, and a molybdenum catalyst.

[0024] In a further aspect, a method for manufacturing artemisinin is provided, comprising the steps of: forming a mixture by mixing ingredients comprising the compound of Formula 5b and the compound of Formula 8a, to form the intermediate of Formula 9a:



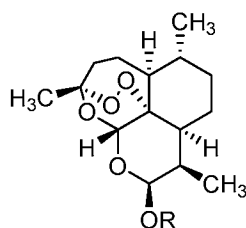
[0025] forming a mixture by mixing ingredients comprising the intermediate of Formula 9a, hydrogen peroxide, and a palladium catalyst, to form the intermediate of Formula 10a:

**10a**

[0026] and forming a mixture by mixing ingredients comprising the intermediate of Formula 10a, hydrogen peroxide, and a catalyst comprising molybdenum, wherein R^c is alkyl, and R^d is alkyl.

5 DETAILED DESCRIPTION

[0027] The present application is based on the discovery of a novel, alternative approach to synthesizing artemisinin (**1**) and its congeners, such as compounds (**2a-d**). The synthesis described herein allows for the cost-effective preparation of artemisinin (**1**) by reducing production time and cost while increasing the availability
 10 of ACT, the most effective treatment against malaria. .

**(2)**

Artemether: $R = -CH_3$ (**2a**)

Arteether: $R = -CH_2CH_3$ (**2b**)

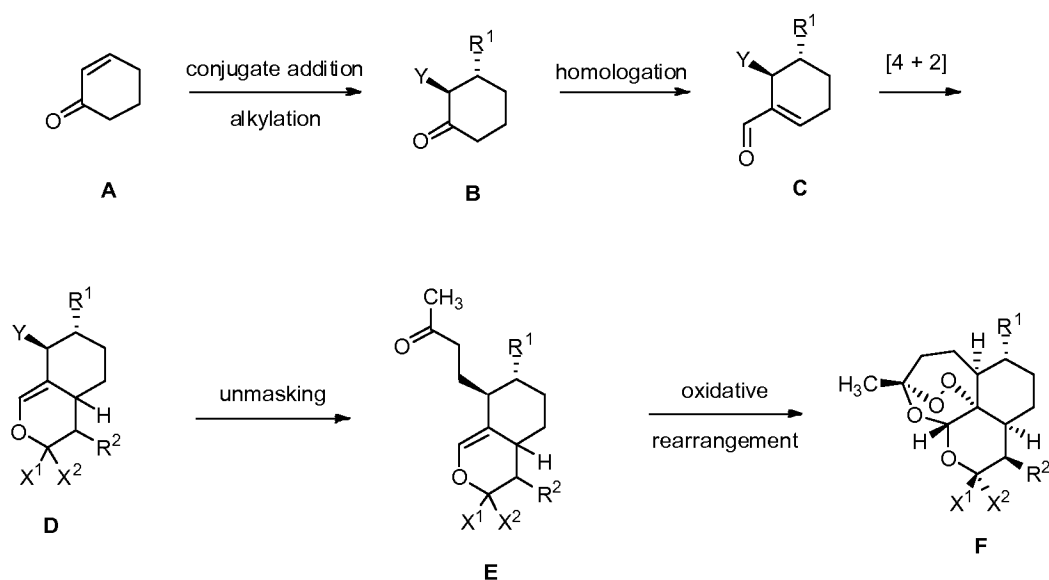
15 Artesunate: $R = -C(O)(CH_2)_2CO_2Na$ (**2c**)

Dihydroartemisinin: $R = H$ (**2d**)

[0028] This approach provides a step-economical [5] method for the low-cost production of artemisinin (**1**) and its derivatives. In order to realize a strategy based
 20 on cheap, readily available chemical inputs, step economy, and overall efficiency,

the use of protecting groups is minimized and cascade reactions are relied on to build in significant molecular complexity at each synthetic step.

[0029] In a first aspect, a synthetic method is provided as outlined below in Scheme 1:



R^1 = alkyl

R^2 = -H, -CH₃, alkyl, cycloalkyl, heterocycle, aryl

At least one of X^1 and X^2 = -H, -OH, -OMe, -OEt, -OSiR'₃ (where R' = alkyl) or any other alcohol-protecting group. Also, X^1 may be =O, with no X^2 present

Y = masked -CH₂CH₂C(O)CH₃

Scheme 1

[0030] Cyclohexenone **A** is alkylated and reacted with an MVK equivalent to yield a synthetic intermediate of Formula **B**. The alkylation can be carried out with an alkylating agent. Example alkylating agents include organometallic compounds such as organozinc compounds. For instance, the alkylating agent may be dimethylzinc (or diethylzinc) in a copper-catalyzed 1,4-addition to cyclohexenone. The alkylation may be carried out in the presence of a chiral ligand such as a chiral phosphoramidite. The MVK equivalent may be one of those listed in Table 1, such as the Stork-Jung vinyl silane [22] or crotyl bromide, or any other four-carbon unit capable of becoming a methyl ketone.

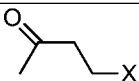
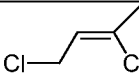
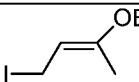
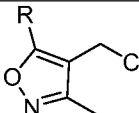
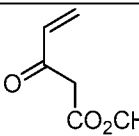
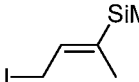
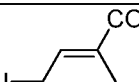
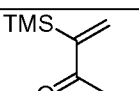
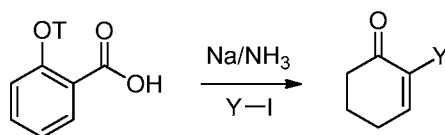
MVK Equivalent	Reference(s) Disclosing MVK Equivalent
 $X = \text{NR}_2, \text{N}^+\text{R}_3, \text{Cl}$	Robinson, <i>J. Chem. Soc.</i> 1937 , 53. Theobald, <i>Tetrahedron</i> 1966 , 22, 2869. Halsall <i>J. Chem. Soc.</i> 1964 , 1029.
	Julia, <i>Bull. Soc. Chim. Fr.</i> 1954 , 5, 780.
	Stork, <i>J. Am. Chem. Soc.</i> 1956 , 78, 501
	Stork, <i>J. Am. Chem. Soc.</i> 1967 , 89, 5461 and 5463
	Stork, <i>Tetrahedron Lett.</i> 1972 , 2755. Wenkert, <i>J. Am. Chem. Soc.</i> 1964 , 86, 2038.
	Stork, <i>J. Am. Chem. Soc.</i> 1974 , 96, 3682.
	Stotter, <i>J. Am. Chem. Soc.</i> 1974 , 96, 6524.
	Stork, <i>J. Am. Chem. Soc.</i> 1973 , 95, 6152. Boeckman, <i>J. Am. Chem. Soc.</i> 1973 , 95, 6867.

Table 1

[0031] Crotyl bromide is an advantageous MVK equivalent due to its low cost. The methylation and the reaction with crotyl bromide may be carried out as a one-pot conjugate addition/alkylation, which is believed to occur by a mechanism whereby the copper or zinc enolate formed by the conjugate addition is alkylated with an MVK equivalent such as crotyl bromide.

[0032] An intermediate of Formula **B** may also be obtained according to the procedure of Scheme 2 [29]:



Scheme 2

[0033] where T is an alkyl group, such as methyl, and –Y may be, for instance, –CH₂CH₂CH=CH₂. The product of Scheme 2 may then be alkylated, for example with an organozinc alkylating agent, to yield an intermediate of Formula **B**.

[0034] Next, intermediate **B** is homologated to the α,β-unsaturated aldehyde intermediate **C**. The homologation may be carried out through a one-step process, but higher yields have been achieved through a two-step Shapiro process. In the first step, intermediate **B** is reacted with p-toluenesulfonylhydrazide to obtain a p-toluenesulfonylhydrazone. The p-toluenesulfonylhydrazone is then reacted with a strong base, such as n-butyllithium (n-BuLi), and dimethylformamide, to yield **C**.

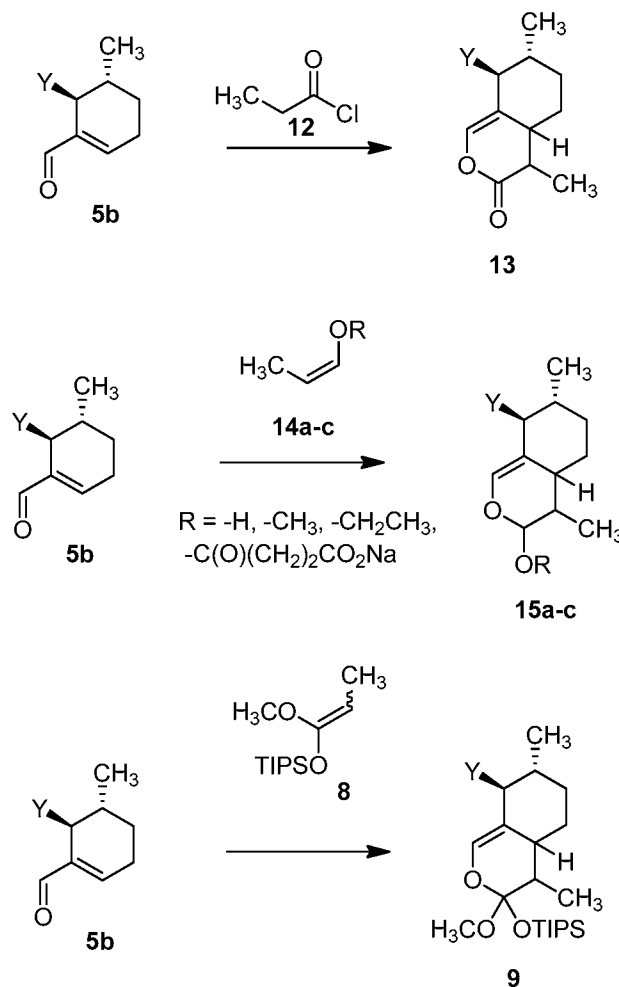
[0035] The Y moiety may then be “unmasked,” that is converted to –CH₂CH₂C(O)CH₃. In instances where the Y moiety is a –CH₂CH=CHCH₃ or –CH₂CH₂CH=CH₂ group, the unmasking may be carried by an oxidation reaction.

Alternatively, the unmasking may be carried out at a later stage in the synthesis, for example right prior to the synthetic step leading to the formation of the endoperoxide bridge moiety.

[0036] Intermediate **C**, which may bear the unmasked –CH₂CH₂C(O)CH₃ group instead of moiety Y, is then reacted with a dienophile in a [4+2] reaction yielding an intermediate of Formula **D**, where the nature of moieties X₁ and X₂ depends on the dienophile employed. For example, when the dienophile is a silyl ketene acetal, such as **8**, the product **D** is an *ortho* ester, such as **9** (Scheme 3). A dienophile bearing a carbonyl group, such as propionyl chloride **12**, will instead yield a lactone such as **13**, where X₁ is a carbonyl oxygen and no X₂ is present (Scheme 3). In another example, the dienophile is a vinyl ether **14a-c** that may be used to synthesize **2a-c** via compounds **15a-c** (Scheme 3).

[0037] The [4+2] reaction may be carried out in the presence of additional compounds, including: catalysts, for instance Lewis acids such as aluminum salts; bases, for example when required to generate dienophile enolates; and other compounds that may be used to promote and/or control [4+2]-type reactions (e.g.,

the Diels-Alder reaction). Among Lewis acids, dialkylaluminum chloride salts have been found to preferentially catalyze the formation of the desired products relative to other reactions.



Scheme 3

[0038] The Y moiety is now unmasked to $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{CH}_3$, if this conversion has not been carried out prior to the formation of **D**. The specific chemistry of the unmasking reaction(s) depends on the type of Y moiety present in **D**, and is therefore dependent on the MVK equivalent chosen in the above synthesis of **B**. As set for above, for instance, the unmasking may be carried out by subjecting **D** to an oxidation to yield an intermediate of Formula **E**.

[0039] This oxidation may be carried out with a peroxide oxidizer in the presence of a palladium catalyst. Example peroxide oxidizers include hydrogen peroxide (H_2O_2)

and organic peroxides such as tert-butyl hydroperoxide (tBuOOH). Example palladium catalysts include palladium salts such as PdCl₂.

[0040] Then, **E** is subjected to an oxidative rearrangement to yield a product of Formula **F**. The oxidative rearrangement may be accomplished with singlet oxygen which may be generated *in situ* from hydrogen peroxide in the presence of a metal catalyst. The metal in the metal catalyst may be selected from lanthanum, cerium, molybdenum, calcium, tungsten, scandium, titanium, zirconium, vanadium, and combinations thereof. Example molybdenum catalysts include ammonium molybdate, ammonium heptamolybdate, molybdic acid, molybdic oxide, molybdenum trioxide, barium molybdate, calcium molybdate, iron molybdate, lead molybdate, potassium molybdate and strontium molybdate. In particular, ammonium molybdate ((NH₄)₂MoO₄) has been found to produce the highest yields of desired products.

Example 1

[0041] As illustrated in Figure 2, the example synthesis of artemisinin (**1**) began with the conversion of cyclohexenone **4** to ketone **7** in 61% yield (7:1 trans:cis, 91% enantiomeric excess) via a one-pot conjugate addition/alkylation sequence [24] relying on crotyl bromide as a cost-effective MVK equivalent. The treatment of cyclohexanone **7** with p-toluenesulfonylhydrazide in methanol at room temperature provided the corresponding hydrazone. After replacing the solvent, exposure of the hydrazone to n-BuLi at low temperature provided a vinyl anion that was quenched with dimethylformamide [25]. This one-pot sequence resulted in the production of α,β-unsaturated aldehyde **5b** in 72% overall yield.

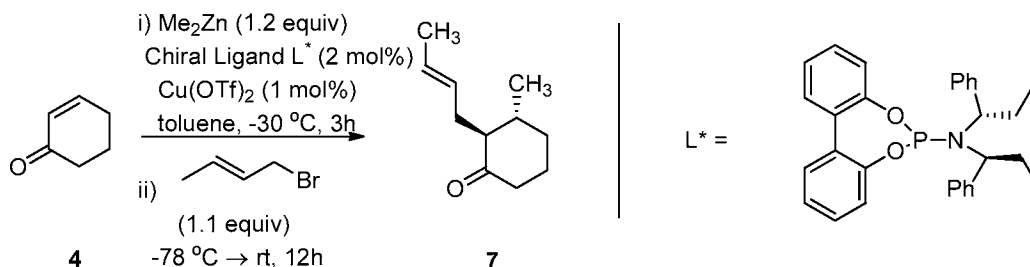
[0042] A novel [4+2] reaction was developed for the installation of the six-membered lactone of artemisinin (**1**). An extensive investigation of acid catalysts revealed the ability of dialkylaluminum chloride salts to preferentially catalyze the formation of the [4+2] product relative to alternate pathways leading to Mukaiyama aldol or Michael products [26, 27]. In particular, it was found that the reaction of silyl ketene acetal **8** and **5b** in the presence of dimethyl- or diethylaluminum chloride provides *ortho* ester **9** in ≥95% yield as a mixture of four diastereomers (10:4:1:1).

[0043] Extensive experimentation lead to the discovery that by stirring *ortho* ester **9** in aqueous hydrogen peroxide with a palladium catalyst, the internal olefin moiety of

9 is oxidized in greater than 90% yield, producing methyl ketone **10** in 61% yield and the ethyl ketone in approximately 30% yield (product not shown). While these conditions provided the fewest number of side products, extended reaction times were found to achieve full conversion. The incorporation of co-solvents or phase-transfer catalysts to enhance solubility resulted in increased conversion when compared to water alone.

[0044] In an effort to convert methyl ketone **10** to artemisinin (**1**), a number of disparate oxidative rearrangement strategies were evaluated. Higher yields were obtained by subjecting **10** to the combination of ammonium molybdate and hydrogen peroxide. Without being bound to any particular theory, it is believed that this final oxidative rearrangement utilizes the *in situ* formation of singlet oxygen from the decomposition of H_2O_2 by ammonium molybdate to oxidize the enol olefin moiety of **10** [28]. Again without being bound to any particular theory, it is believed that, following oxidation, several oxidized intermediates converge to artemisinin (**1**) with a yield of 29-42% in the presence of acid.

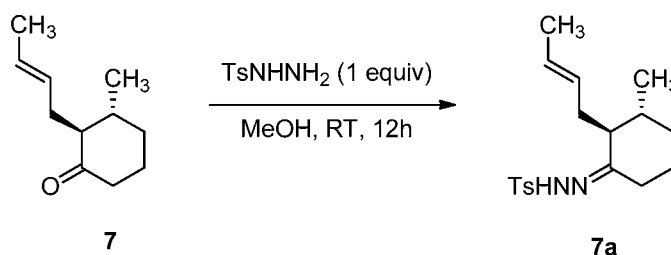
EXPERIMENTAL



[0045] To a flame-dried flask was added $\text{Cu}(\text{OTf})_2$ (0.94 grams (g), 2.6 millimoles (mmol)), phosphoramidite ligand L^* (2.4 g, 5.2 mmol) and anhydrous toluene (500 mL) under a nitrogen atmosphere. This mixture was stirred for 30 minutes (min) at room temperature and then to which cyclohex-2-enone **4** (25 g, 260 mmol) was added. The mixture was stirred at room temperature for 20 min before cooling to $-30\text{ }^\circ\text{C}$, then dimethylzinc (260 mmol) was added to the solution. The reaction was stirred at $-30\text{ }^\circ\text{C}$ until complete consumption of starting material which was indicated by TLC (usually 3 hours (h)). Then, the above solution was cooled $-78\text{ }^\circ\text{C}$ before crotyl bromide (38.6 g, 286 mmol) was added. The reaction was allowed to come to room temperature over 4 hours and stirred for additional 8 hours before 300 mL saturated aqueous ammonium chloride was added at $0\text{ }^\circ\text{C}$. The organic

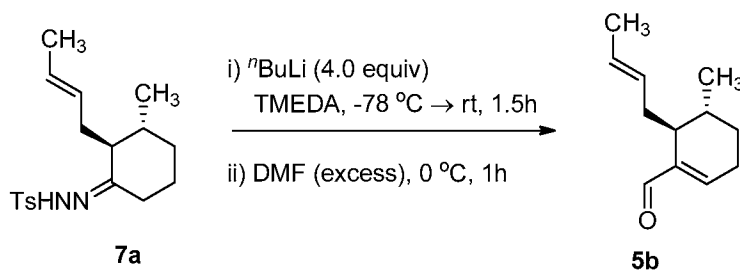
phase was separated and the aqueous phase was extracted twice with 300 mL hexanes, then the combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo*. The dark red crude mixture was purified by flash chromatography (hexanes/ethyl acetate, 20/1) to afford desired product **7** as pale yellow oil.

[0046] Yield 26 g, 61% and 7/1 dr. IR (film) ν/cm^{-1} 2929 (s), 2870 (m), 1711 (s), 1454 (m), 971 (m). $[\alpha]_D^{20} = +28.1$ (c 0.980, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 5.36-5.49 (m, 2H), 2.30-2.40 (m, 2H), 2.21-2.28 (m, 2H), 2.00-2.06 (m, 1H), 1.94-1.99 (m, 1H), 1.82-1.88 (m, 1H), 1.60-1.75 (m, 5H), 1.39-1.49, (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 212.6, 128.9, 126.4, 57.2, 41.5, 37.6, 33.2, 29.8, 25.4, 20.3, 17.9. CI-HRMS calculated for $\text{C}_{11}\text{H}_{19}\text{O}$ $[\text{M} + \text{H}]$ 167.1430, found 167.1433.



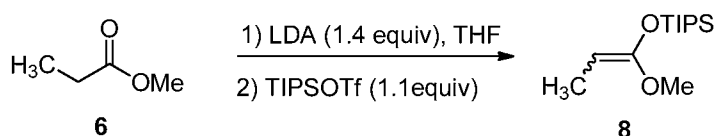
[0047] To a solution of ketone **7** (26 g, 157 mmol) in 100 mL MeOH was added TsNHNH₂ (29 g, 157 mmol) at 0 °C. The reaction was allowed to come to room temperature over 2 hours and stirred for additional 10 hours before concentrated *in vacuo*. The sticky crude mixture could be used without further purification or be purified by flash chromatography (hexanes/ethyl acetate, 20/1) to afford desired product as white sticky gum.

[0048] IR (film) ν/cm^{-1} 3225 (s), 2938 (s), 1705 (m), 1599 (m), 1163 (m), 812 (m). $[\alpha]_D^{20} = +38.9$ (c 0.79, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.72 (brs, 1H), 7.27 (d, $J = 8.4$ Hz, 2H) 5.35-5.44 (m, 1H), 5.04-5.11 (m, 1H), 2.49-2.53 (m, 1H), 2.39 (s, 3H), 2.09-2.29 (m, 5H), 1.89-1.96 (m, 1H), 1.69-1.78 (m, 1H), 1.59-1.61 (m, 1H), 1.45 (d, $J = 6.4$ Hz, 2H), 1.38-1.42 (m, 1H), 1.25-1.29 (m, 1H), 0.77 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 163.0, 143.6, 135.4, 129.3, 129.1, 128.1, 125.7, 50.6, 35.3, 32.1, 31.2, 25.6, 23.0, 21.5, 19.6, 17.7. ESI-TOF-HRMS calculated for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]$ 357.1793, found 335.1781.



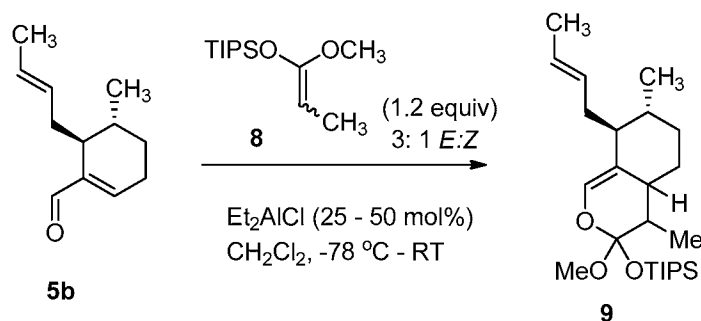
[0049] To a stirred solution of 1.6 M n-butyllithium (n-BuLi) (392 mL, 628 mmol) was slowly added a solution of hydrazide in 300 mL tetramethylethylenediamine (TMEDA) at -78°C over 15 minutes. Then, the reaction was warmed to room temperature and stirred at room temperature for 90 minutes before the addition of 60 mL DMF at 0°C . The resulting mixture was stirred at 0°C for 1 hour before 300 mL saturated aqueous ammonium chloride being added at 0°C . The organic phase was separated and the aqueous phase was extracted twice with 300 mL hexanes, then the combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo*. The dark yellow crude mixture was purified by flash chromatography (hexanes/ethyl acetate, 10/1 eluent) to afford desired product **5b** as pale yellow oil. Yield 20 g, 72% from ketone.

[0050] IR (film) ν/cm^{-1} 2957 (m), 2931 (s), 2873 (w), 1685 (s), 1639 (m), 1167(m), 968 (m). $[\alpha]_{\text{D}}^{20} = -45.2$ (c 1.1, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ 9.38 (s, 1H), 6.76 (d, $J = 3.6$ Hz, 1H), 5.36-5.39 (m, 2H), 2.27-2.30 (m, 3H), 1.91-1.98 (m, 2H), 1.72-1.81 (m, 1H), 1.63-1.66 (m, 4H), 1.36-1.42 (m, 1H), 0.86 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 194.6, 151.4, 143.5, 129.4, 126.5, 37.8, 36.3, 27.5, 23.7, 23.0, 18.5, 17.9. CI-HRMS calculated for $\text{C}_{12}\text{H}_{19}\text{O}$ $[\text{M} + \text{H}]$ 179.1430, found 179.1429.



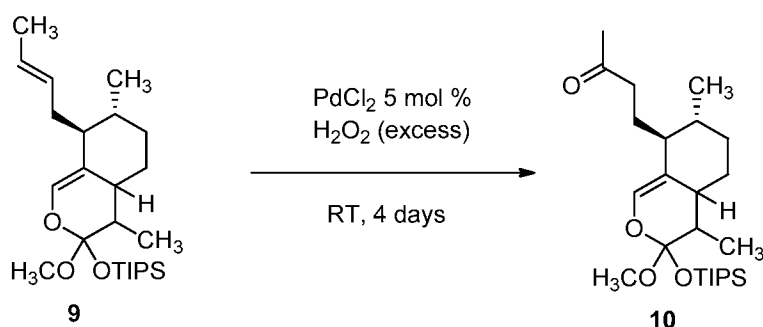
[0051] To a solution of diisopropylamine (0.75 g, 7.5 mmol) in THF (10 mL) was added 2.5 M nBuLi (2.8 mL, 7 mmol) at 0°C . The resulting mixture was stirred for 30 minutes at 0°C before methyl propionate **6** (0.44 g, 5 mmol) was added at -78°C . After stirring at -78°C for 90 min, TIPSOTf (1.69 g, 5.5 mmol) was added to the reaction. The reaction mixture was allowed to come to room temperature over 2

hours and then filtered through a pad of aluminum to yield a colorless solution which was concentrated *in vacuo*. The crude product **8** was used without further purification.



5 **[0052]** To a solution of the unsaturated aldehyde **5b** (20.0 g, 113 mmol) and silyl ketene acetal **8** (33 g, 135 mmol) in DCM (120 mL) was added Et₂AlCl (28 mmol) at -78 °C. The reaction mixture was allowed to come to room temperature over 2 hours and then stirred at room temperature for 12 hours before 200 mL saturated aqueous ammonium chloride being added at 0 °C. The organic phase was
10 separated and the aqueous phase was extracted twice with 200 mL ethyl acetate, then the combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. The yellow crude mixture was filtered through silica (hexanes/ethyl acetate, 10/1 eluent) to afford desired product **9** as pale yellow oil. Yield: 47 g, >98%.

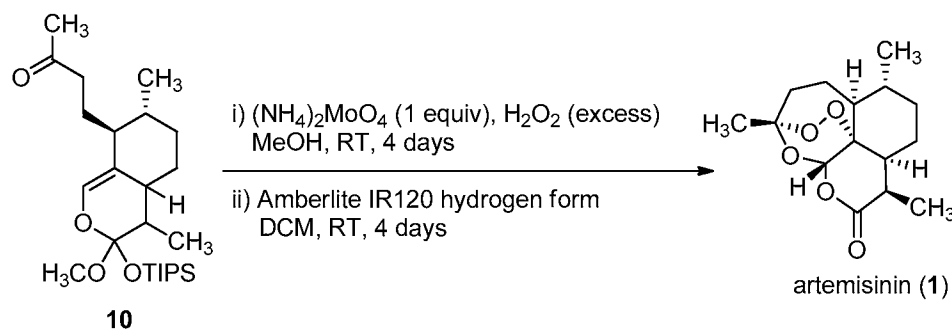
[0053] IR (film) ν/cm^{-1} 3429 (s), 2944 (s), 2867 (s), 1739 (s), 1651 (s), 1462 (m),
1159 (s), 882 (m). $[\alpha]_{\text{D}}^{20} = +45.2$ (c 0.970, CHCl_3). ^1H NMR (400 MHz, CDCl_3) δ
6.30 (s, 1H), 5.37-5.42 (m, 2H), 3.67 (s, 3H), 2.66-2.75 (m, 2H), 2.08-2.12 (m, 3H),
1.70-1.85 (m, 3H), 1.61-1.62 (m, 2H), 1.05-1.18 (m, 27H), 0.89 (d, $J = 7.2$ Hz, 3H).
 ^{13}C NMR (100 MHz, CDCl_3) δ 178.0, 138.2, 131.3, 125.3, 116.1, 51.4, 42.3, 41.6,
38.9, 38.2, 31.1, 24.5, 23.8, 19.5, 17.9, 17.7, 17.0, 11.9. ESI-TOF-HRMS
calculated for $\text{C}_{25}\text{H}_{46}\text{O}_3\text{NaSi}$ $[\text{M} + \text{Na}]$ 445.3114, found 445.3133.



[0054] To a mixture of PdCl₂ (0.315 g, 1.8 mmol) and olefin **9** (15 g, 35 mmol) was added 35% H₂O₂ (50 mL, 15 equiv) at room temperature. Due to the heterogeneous nature of the reaction, vigorous stirring was applied. Additional H₂O₂ (1-2 equiv) was added to the reaction at once every 24 h. The reaction mixture was stirred for four days before being partitioned between ethyl acetate (200 mL) and water (100 mL). The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo* to give crude mixture containing a 2:1 mixture of methyl:ethyl ketone. Desired product **10** was isolated by flash chromatography (hexanes/ethyl acetate 10/1 eluent) in 61% yield (9.4 g). The ethyl ketone was also recovered in 31% yield.

[0055] NOTE: The reaction could also be run with 50% H₂O₂. Some batches of H₂O₂ led to significantly compromised yields (~30% overall). In such cases, the addition of a catalytic amount of butylhydroxytoluene (BHT) could often overcome this issue.

15 **[0056]** IR (film) ν/cm^{-1} 3437 (s), 2893 (m), 2867 (s), 1738 (s), 1719 (m), 1649 (m),
1462 (m), 1159 (s), 882 (m). $[\alpha]_{\text{D}}^{20} = +59.4$ (c 0.870, CHCl_3). ^1H NMR (500 MHz,
 CDCl_3) δ 6.36 (s, 1H), 3.67 (s, 3H), 2.66-2.72 (m, 1H), 2.57-2.61 (m, 1H), 2.40-2.55
(m, 2H), 2.09-2.14 (m, 1H), 2.10 (s, 3H), 1.81-1.88 (m, 1H), 1.69-1.77 (m, 3H), 1.61-
1.67 (m, 1H), 1.26-1.32 (m, 1H), 1.12-1.19 (m, 4H), 1.06-1.08 (m, 18H), 1.02 (d, $J =$
20 6.5 Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ 209.2, 177.9,
139.0, 115.4, 51.4, 43.2, 42.4, 41.6, 38.6, 33.1, 29.8, 29.1, 24.7, 24.2, 19.7, 17.7,
17.0, 11.9. ESI-TOF-HRMS calculated for $\text{C}_{25}\text{H}_{46}\text{O}_4\text{NaSi}$ $[\text{M} + \text{Na}]$ 461.3063, found
461.3052.



[0057] To a solution of compound **10** (7 g, 15.4 mmol) and ammonium molybdate (1.51 g, 7.7 mmol) in t-BuOH (60 mL) was added 50% H₂O₂ (10 mL, 150 mmol).

The solution was stirred with additional H₂O₂ (5 mL, 75 mmol) added every 12 hours. At 72 hours, the mixture was diluted with water (100 mL), extracted with CH₂Cl₂ (3x100 mL), dried over MgSO₄, filtered and concentrated. The yellow crude mixture was dissolved in DCM (50 mL) and treated with p-toluensulfonic acid (pTSA) (285 mg, 1.5 mmol). The resulting solution was stirred for 72 hours before being concentrated and filtered through a plug of silica (hexanes/diethyl ether 10:1 eluent). The resulting yellow oil could be purified by flash chromatography (ethyl acetate in hexanes 0% to 20%), or recrystallized from heptane to obtain 1.26 g artemisinin (**1**) (29% yield).

[0058] NOTE: Amberlite IR120 hydrogen form and other homogenous proton sources could also be used in place of p-toluenesulfonic acid.

[0059] IR (film) ν/cm^{-1} 2956 (m), 2933 (m), 2884 (m), 2861 (m), 1739 (s), 1201 (m), 1114 (s), 1033 (m), 1028 (m), 995 (s), 883 (m). $[\alpha]_{\text{D}}^{20} = +64.0$ (c 1.20, CHCl₃) (nat. $[\alpha]_{\text{D}}^{20} = +66.6$ (c 0.90, CHCl₃)). ¹H NMR (400 MHz, CDCl₃) δ 5.84 (s, 1H), 3.38 (dq, $J = 7.4, 5.5$ Hz, 1H), 2.41 (ddd, $J = 14.4, 12.9, 3.9$ Hz, 1H), 2.06-1.92 (m, 2H), 1.90-1.82 (m, 1H), 1.79-1.70 (m, 2H), 1.52-1.31 (m, 3H), 1.42 (s, 3H), 1.18 (d, $J = 7.4$ Hz, 3H), 1.10-1.00 (m, 2H), 0.98 (d, $J = 5.9$ Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 172.7, 106.0, 94.3, 80.1, 50.7, 45.6, 38.2, 36.5, 34.2, 33.5, 25.8, 25.5, 24.0, 20.5, 13.2. HRMS calculated for C₁₅H₂₂O₅Na [M+ Na] 305.1365, found 305.1356.

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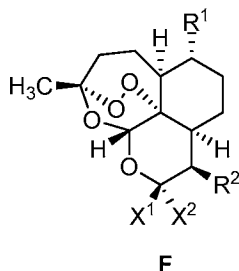
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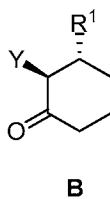
CLAIMS

1. A method for manufacturing molecules of Formula F:



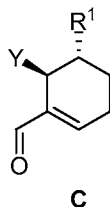
the method comprising the steps of:

- 5 forming a mixture by mixing ingredients comprising cyclohexenone, an alkylating agent, and an MVK equivalent, to form a first synthetic intermediate of Formula B:

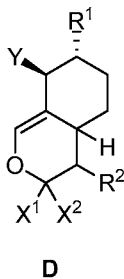


wherein R¹ is an alkyl moiety and Y is a masked –CH₂CH₂C(O)CH₃ moiety;

- 10 homologating the intermediate of Formula B to an aldehyde intermediate of Formula C:



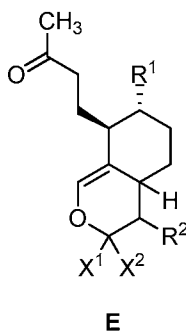
forming a mixture by mixing ingredients comprising the intermediate of Formula C and a dienophile, to form an intermediate of Formula D:



wherein: R^2 is selected from the group consisting of -H, alkyl, cycloalkyl, heterocycle, and aryl, and

at least one of X_1 and X_2 is selected from the group consisting of -H, -OH, -OCH₃, -OCH₂CH₃, -OSiR', -OR'', and carbonyl oxygen, wherein R' is alkyl and R'' is alkyl;

converting moiety Y to a -CH₂CH₂C(O)CH₃ group, to form an intermediate of Formula E, and

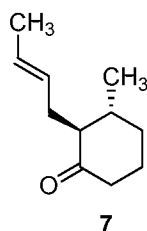


forming a mixture by mixing ingredients comprising the intermediate of Formula E, hydrogen peroxide, and a metal catalyst.

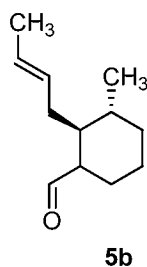
2. The method of claim 1, wherein the alkylating agent is dimethylzinc.
3. The method of claim 1, wherein the MVK equivalent is crotyl bromide.
4. The method of claim 1, wherein the homologating the intermediate of Formula B to the aldehyde intermediate of Formula C comprises forming a mixture comprising the intermediate of Formula B and p-toluenesulfonylhydrazide.
5. The method of claim 1, wherein the dienophile is selected from the group consisting of CH₃CH₂C(O)Cl, (CH₃O)(TIPSO)CH=CHCH₃, and CH₃CH=CHOR, wherein R is selected from the group consisting of -H, -CH₃, -CH₂CH₃, and -C(O)(CH₂)₂CO₂Na.
6. The method of claim 1, wherein the mixture comprising the intermediate of Formula C and the dienophile further comprises a dialkylaluminum chloride.
7. The method of claim 1, wherein the converting moiety Y to a -CH₂CH₂C(O)CH₃ group comprises forming a mixture by mixing ingredients comprising the intermediate of Formula D, a peroxide oxidizer, and a palladium catalyst.

8. The method of claim 1, wherein the metal catalyst comprises a metal selected from the group consisting of lanthanum, cerium, molybdenum, calcium, tungsten, scandium, titanium, zirconium, vanadium, and combinations thereof.
9. The method of claim 1, wherein the metal catalyst comprises molybdenum.
10. A method for manufacturing artemisinin, comprising the steps of:

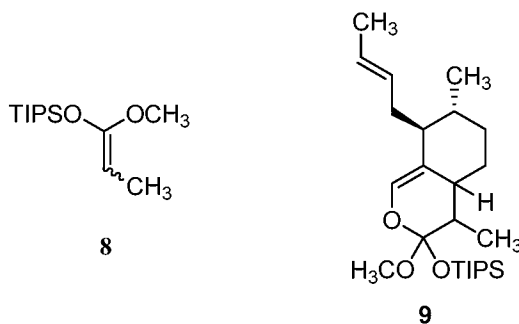
forming a mixture by mixing ingredients comprising cyclohexenone, a methylating agent, and crotyl bromide, to form a first synthetic intermediate of Formula 7:



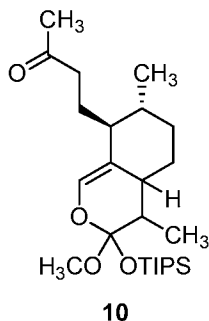
- homologating the intermediate of Formula 7 to an aldehyde intermediate of Formula 5b:



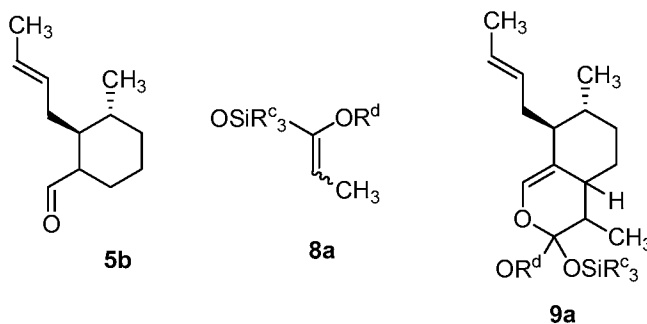
forming a mixture by mixing ingredients comprising the intermediate of Formula 5b and a compound of Formula 8, to form an intermediate of Formula 9:



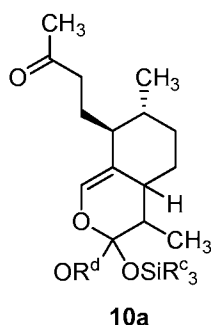
forming a mixture by mixing ingredients comprising the intermediate of Formula 9, hydrogen peroxide, and a palladium catalyst, to form an intermediate of Formula 10:



- 5 and forming a mixture by mixing ingredients comprising the intermediate of Formula 10, hydrogen peroxide, and a molybdenum catalyst.
11. The method of claim 10, wherein the methylating agent is dimethylzinc.
12. The method of claim 10, wherein the homologating the intermediate of Formula 7 to the aldehyde intermediate of Formula 5b comprises forming a mixture
 - 10 comprising the intermediate of Formula 7 and p-toluenesulfonylhydrazide.
13. The method of claim 10, wherein the mixture comprising the intermediate of Formula 5b and the compound of Formula 8 further comprises a dialkylaluminum chloride.
14. The method of claim 13, wherein the dialkylaluminum chloride is
 - 15 diethylaluminum chloride.
15. The method of claim 10, wherein the palladium catalyst in the mixture comprising the intermediate of Formula 9, hydrogen peroxide, and a palladium catalyst is palladium chloride.
16. The method of claim 10, wherein the molybdenum catalyst is $(\text{NH}_4)_2\text{MoO}_4$.
- 20 17. A method for manufacturing artemisinin, comprising the steps of:
 - forming a mixture by mixing ingredients comprising the compound of Formula 5b and the compound of Formula 8a, to form the intermediate of Formula 9a:



forming a mixture by mixing ingredients comprising the intermediate of Formula 9a, hydrogen peroxide, and a palladium catalyst, to form the intermediate of Formula 10a:



and forming a mixture by mixing ingredients comprising the intermediate of Formula 10a, hydrogen peroxide, and a catalyst comprising molybdenum, wherein R^c is alkyl, and R^d is alkyl.

18. The method of claim 17, wherein the catalyst comprising molybdenum is a molybdenum salt.

19. The method of claim 17, wherein the catalyst comprising molybdenum is $(\text{NH}_4)_2\text{MoO}_4$.

20. The method of claim 17, wherein R^c is an $-\text{CH}(\text{CH}_3)_2$ moiety, and R^d is a $-\text{CH}_3$ moiety.

1/2

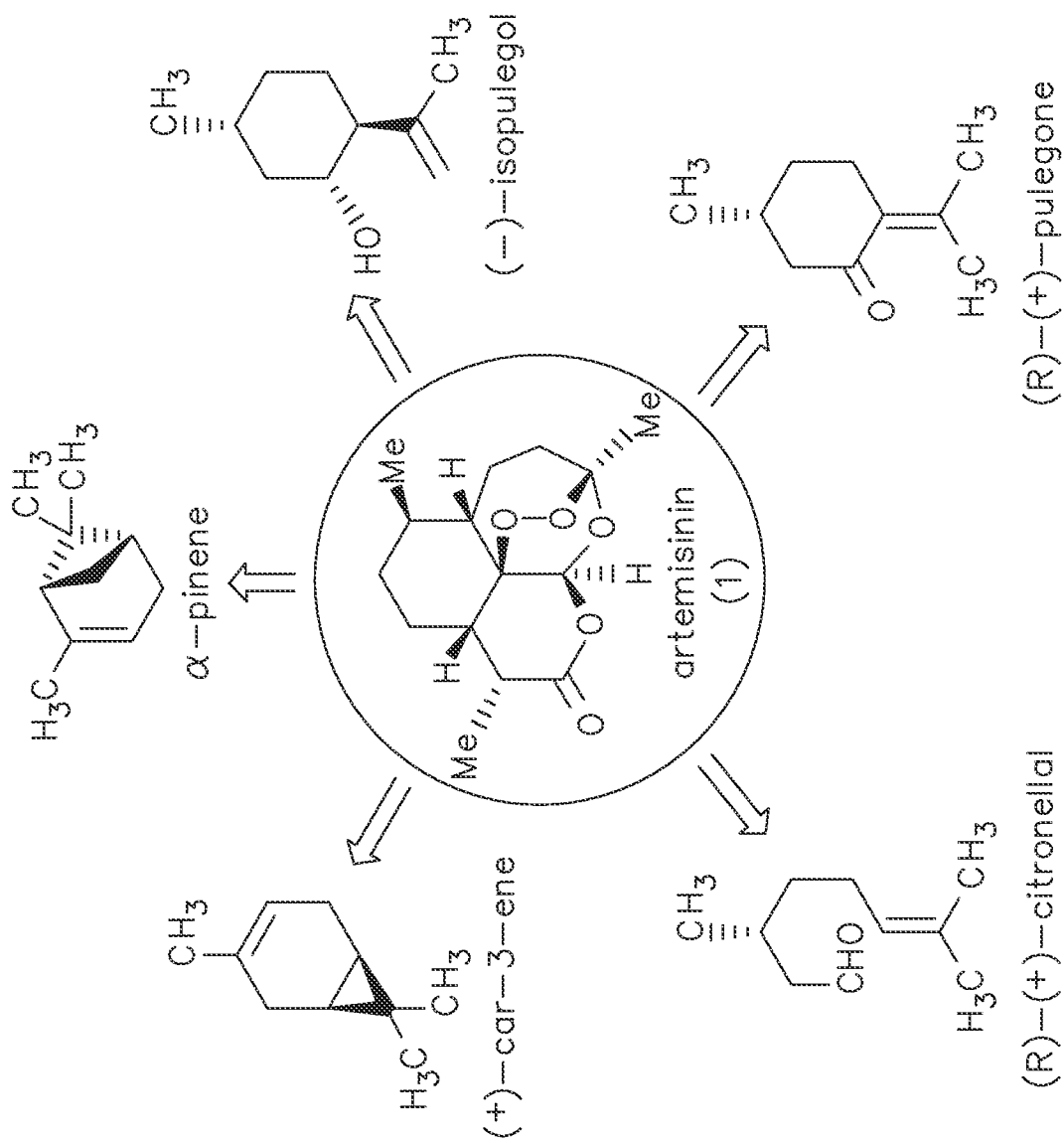


Fig. 1

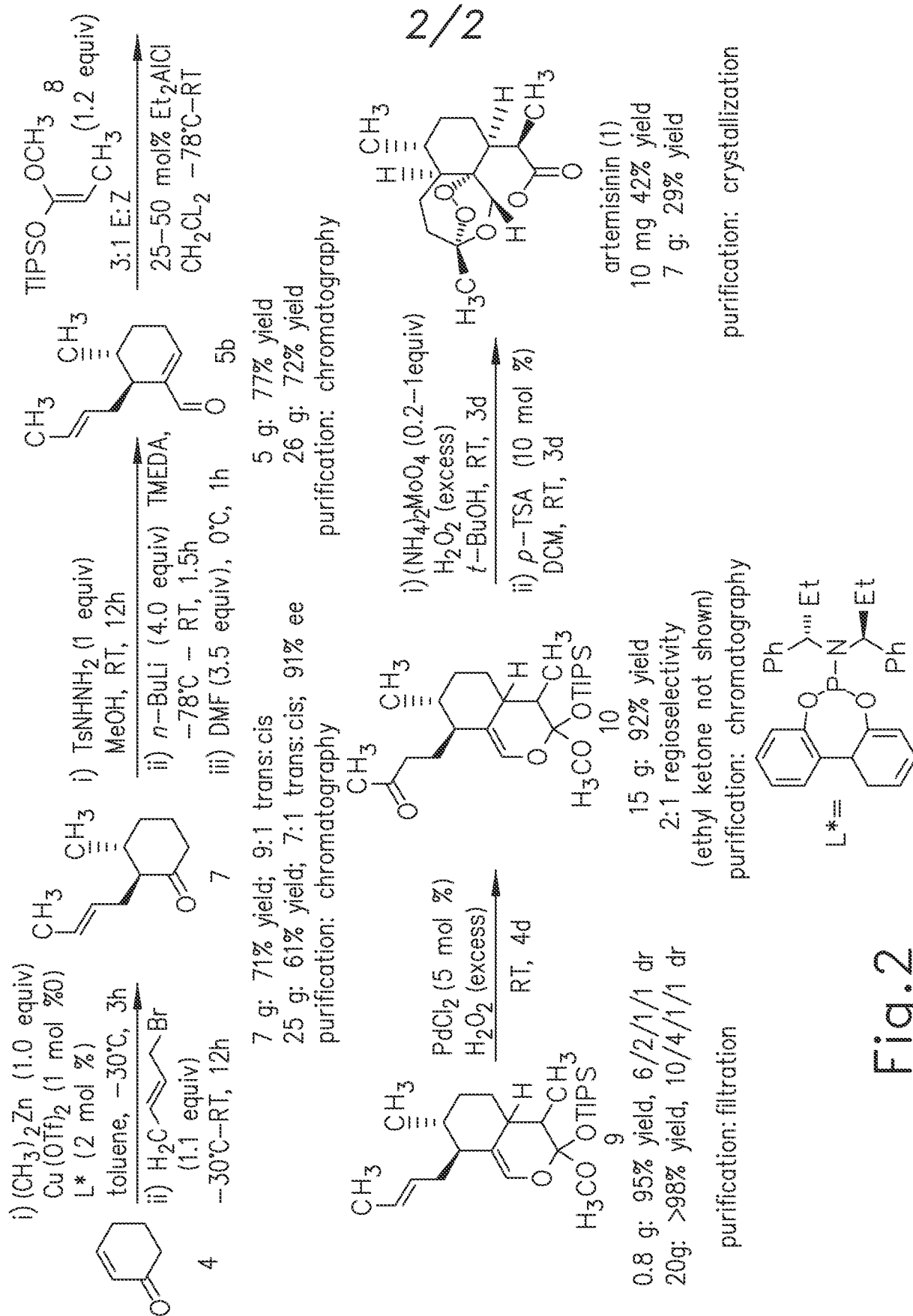


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/037214

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D493/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHANG HO OH ET AL: "A Short Synthesis of 6,9-Desmethyldexoartemisinin and Its Isomer", BULLETIN OF THE KOREAN CHEMICAL SOCIETY, KOREAN CHEMICAL SOCIETY, SEOUL, KR, vol. 17, no. 7, 1 January 1996 (1996-01-01), pages 581-582, XP007920741, ISSN: 0253-2964 Scheme 1; page 581 ----- -/--	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

22 June 2012

Date of mailing of the international search report

02/07/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lewis, Sara

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/037214

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GARY H. POSNER ET AL: "Orally Active, Water-Soluble Antimalarial 3-Aryltrioxanes: Short Synthesis and Preclinical Efficacy Testing in Rodents", JOURNAL OF MEDICINAL CHEMISTRY, vol. 45, no. 18, 29 August 2002 (2002-08-29), pages 3824-3828, XP55030521, ISSN: 0022-2623, DOI: 10.1021/jm020210h Scheme 2	1-20
A	----- FALMAI BINNS ET AL: "An unsuccessful approach to the framework of the antimalarial, arteether", TETRAHEDRON LETTERS, vol. 30, no. 9, 1 January 1989 (1989-01-01), pages 1125-1128, XP55030523, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(01)80377-4 Scheme 2; page 1127 -----	1-20